PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
ROCHE DIAGNOSTICS GMBH
Attn. Schreiner, Siegfried
Patent Department (TR-E)
P.O. Box 11 52
D-82372 Penzberg
GERMANY

Roche Diagnostics GmbH
Patent Department Penzberg
ASK | 19. JUNI 2006 | WN
BK | | WJ
BUR | HH | HIL | MI | SB

Date of mailing (day/month/year): 19/06/2006

Applicant's or agent's file reference: 22393 WO WJ

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.: PCT/EP2005/003348

International filing date (day/month/year): 31/03/2005

Applicant: F.HOFFMANN-LA ROCHE AG

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority:
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer: Joëlle Gerber

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Patent Department (TR-E)		
Case 22393	Int.-Nr.	
Literatur erfasst:	Zeichen:	Datum:
Lit.sheet ☒ Endnote ☒	TW	27.06.06

Roche Diagnostics GmbH
Patent Department Penzberg

ASK	19. JUNI 2006			WN
BK				WW TW
BUR	HH	HIL	MI	SR

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
22393 WO-WJ		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2005/003348	31/03/2005	01/04/2004

Applicant

F.HOFFMANN-LA ROCHE AG

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      ☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box II).

3. ☐ **Unity of invention is lacking** (see Box III).

4. With regard to the **title,**
   ☐ the text is approved as submitted by the applicant.
   ☒ the text has been established by this Authority to read as follows:

   CYCLODEXTRIN INCLUSIONS COMPLEXES OF PYRIMIDINE-2,4,6-TRIONES

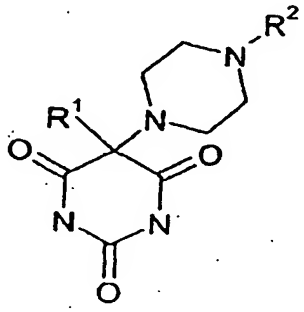
5. With regard to the **abstract,**
   ☐ the text is approved as submitted by the applicant.
   ☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 1
      ☒ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figures is to be published with the abstract.

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

It was surprisingly found that a trioxopyrimidine-cyclodextrin complex formed of a trioxopyrimidine derivative represented by the below-described formula (I) and a water-soluble cyclodextrin (further abbreviated as CD) exhibits enhanced water solubility, excellent stability, and low topical stimulation and is useful as a therapeutic agent.

Accordingly, the present invention provides a trioxopyrimidine-cyclodextrin complex formed of a trioxopyrimidine derivative or a salt thereof and a cyclodextrin, preferably α-, β- or γ-cyclodextrin or a water-soluble cyclodextrin derivative (water-soluble being defined as a solubility of at least 0.5 gr/100ml water at 25°C), wherein the trioxopyrimidine derivative is represented by formula (I).



(I)

It was furthermore found that such a trioxopyrimidine complex with cyclodextrin and an adjuvant such as L-lysine or L-arginine show improved water solubility and bioavailability, excellent stability, and low topical stimulation and is useful as a therapeutic agent. Accordingly, the present invention provides a trioxopyrimidine-

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/003348

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/48 A61K31/515 A61P11/06 A61K31/198 A61K47/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, CHEM ABS Data, DISSERTATION ABS, CANCERLIT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/25217 A (HOFFMANN LA ROCHE) 12 April 2001 (2001-04-12) cited in the application examples 1,3.1,3.7,3.15	1-10
Y	WO 97/23465 A (BOEHRINGER MANNHEIM GMBH ; BOSIES ELMAR (DE); ESSWEIN ANGELIKA (DE); G) 3 July 1997 (1997-07-03) cited in the application example 26	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 June 2006	19/06/2006

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Dullaart, A

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Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GRAMS F ET AL: "PYRIMIDINE-2,4,6-TRIONES: A NEW EFFECTIVE AND SELECTIVE CLASS OF MATRIX METALLOPROTEINASE INHIBITORS" BIOLOGICAL CHEMISTRY, vol. 382, no. 8, August 2001 (2001-08), pages 1277-1285, XP008009641 ISSN: 1431-6730 cited in the application the whole document	1-10
Y	WO 02/089824 A (HOFFMANN LA ROCHE ; FRIESS THOMAS (DE); SCHEUER WERNER (DE); KRELL HAN) 14 November 2002 (2002-11-14) figures tables claims	1-10
Y	FOLEY L H ET AL: "Novel 5,5-disubstitutedpyrimidine-2,4,6-triones as selective MMP inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 11, no. 8, 23 April 2001 (2001-04-23), pages 969-972, XP002271775 ISSN: 0960-894X the whole document	1-10
Y	MASAHIKO SUZUKI ET AL: "A STUDY OF 1:1 PLUS 1:2 COMPLEXES BETWEEN BARBITURATE AND CYCLODEXTRIN USING THE FREEZING POINT DEPRESSION METHOD" CHEMICAL AND PHARMACEUTICAL BULLETIN, TOKYO, JP, vol. 41, no. 8, 1 August 1993 (1993-08-01), pages 1444-1447, XP000395593 ISSN: 0009-2363 abstract tables 1,2 page 1447	1-10
Y	WO 00/40962 A (KOSAK KEN M) 13 July 2000 (2000-07-13) claim 1	1-10
Y	JOZSEF SZEJTLI: "CYCLODEXTRIN TECHNOLOGY" 1988, KLUWER ACADEMIC PUBLISHERS , DORDRECHT, NL , XP001194813 page 186 - page 306	1-10

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KOIZUMI K ET AL: "[Comparison between interactions of alpha- and beta-cyclodextrin with barbituric acid derivatives]" YAKUGAKU ZASSHI. JOURNAL OF THE PHARMACEUTICAL SOCIETY OF JAPAN. DEC 1974, vol. 94, no. 12, December 1974 (1974-12), pages 1515-1519, XP008034887 ISSN: 0031-6903 abstract table 1 figures	1-10
Y	LOUKAS YANNIS L: "Quantitative structure-binding relationships (QSBR) and artificial neural networks: Improved predictions in drug: Cyclodextrin inclusion complexes" INTERNATIONAL JOURNAL OF PHARMACEUTICS (KIDLINGTON), vol. 226, no. 1-2, 11 September 2001 (2001-09-11), pages 207-211, XP002297397 ISSN: 0378-5173 abstract tables figure 2	1-10
Y	AKI HATSUMI ET AL: "Multimodal inclusion complexes between barbiturates and 2-hydroxypropyl-beta-cyclodextrin in aqueous solution: Isothermal titration microcalorimetry, 13C NMR spectrometry, and molecular dynamics simulation" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 90, no. 8, August 2001 (2001-08), pages 1186-1197, XP002297398 ISSN: 0022-3549 abstract figures tables	1-10
Y	LOPATA A ET AL: "Quantitative structure-stability relationships among inclusion complexes of cyclodextrins I: Barbituric acid derivatives" JOURNAL OF PHARMACEUTICAL SCIENCES 1985 UNITED STATES, vol. 74, no. 2, 1985, pages 211-213, XP001194803 abstract page 211, right-hand column table 1	1-10

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4

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	IWAOKU R ET AL: "Enhanced absorption of phenobarbital from suppositories containing phenobarbital-[beta]-cyclodextrin inclusion complex" CHEMICAL AND PHARMACEUTICAL BULLETIN 1982 JAPAN, vol. 30, no. 4, 1982, pages 1416-1421, XP001194804 abstract page 1416, paragraph MATERIALS figures page 1419, last paragraph - page 1420, last line	1-10
Y	CSABAI KATALIN ET AL: "Interaction of some barbituric acid derivatives with hydroxypropyl-beta-cyclodextrin" INTERNATIONAL JOURNAL OF PHARMACEUTICS, vol. 91, no. 1, 1993, pages 15-22, XP001202117 AMSTERDAM, NL ISSN: 0378-5173 abstract tables figures page 20, right-hand column - page 21, right-hand column, last line	1-10
Y	LEIN, MICHAEL ET AL: "The new synthetic matrix metalloproteinase inhibitor (roche 28-2653) reduces tumor growth and prolongs survival in a prostate cancer standard rat model" ONCOGENE, vol. 21, no. 3, 2002, pages 2089-2096, XP002297399 ISSN: 0950-9232 the whole document	1-10
Y	WO 00/37109 A (EUPHAR GROUP S.R.L; CORVI MORA, PAOLO) 29 June 2000 (2000-06-29) examples claims	1-10
Y	EP 1 018 340 A (TECNIMEDE-SOCIEDADE TECNICO-MEDICINAL, S.A) 12 July 2000 (2000-07-12) examples claims	1-10

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4

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PIEL G ET AL: "Study of the influence of both cyclodextrins and L-Lysine on the aqueous solubility of nimesulide; isolation and characterization of nimesulide-L-Lysine-Cyclodextrin complexes" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 86, no. 4, 1997, pages 475-480, XP002383359 ISSN: 0022-3549 abstract page 478, right-hand column, paragraph DISCUSSION - page 479, right-hand column, last line ; table 3	1-10
Y	MURA P ET AL: "Ternary systems of naproxen with hydroxypropyl-[beta]-cyclodextrin and aminoacids" INTERNATIONAL JOURNAL OF PHARMACEUTICS 24 JUL 2003 NETHERLANDS, vol. 260, no. 2, 24 July 2003 (2003-07-24), pages 293-302, XP002383360 ISSN: 0378-5173 abstract page 295; table 1 page 300, right-hand column, paragraph CONCLUSION - page 301, right-hand column	1-10
P,Y	MURA P ET AL: "Solid-state characterization and dissolution properties of Naproxen-Arginine-Hydroxypropyl-[beta]-cyclodextrin ternary system" EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, vol. 59, no. 1, 2005, pages 99-106, XP002383361 ISSN: 0939-6411 abstract page 105; table 1 page 106, paragraph CONCLUSION	1-10
P,Y	& EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, 28 July 2004 (2004-07-28), doi: 10.1016/j3rjpb.2004.05.005	1-10

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/003348

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU 768309 B2	04-12-2003
		AU 7784900 A	10-05-2001
		BR 0014678 A	23-07-2002
		CA 2385863 A1	12-04-2001
		CN 1374954 A	16-10-2002
		CZ 20021535 A3	13-11-2002
		DE 60018301 D1	31-03-2005
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		JP 2003511376 T	25-03-2003
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		JP 2000505069 T	25-04-2000
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		ZA 9610765 A	17-07-1998
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		CN 1505521 A	16-06-2004
		EP 1387689 A1	11-02-2004
		JP 2004527568 T	09-09-2004
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/003348

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		DE	69909128 D1	31-07-2003
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		HU	0104822 A2	29-05-2002
		IT	MI982745 A1	19-06-2000
		JP	2002532565 T	02-10-2002
		NZ	512795 A	29-08-2003
		PT	1140110 T	28-11-2003
		TR	200101766 T2	21-12-2001
		TW	225791 B	01-01-2005
		ZA	200105223 A	25-09-2002
EP 1018340 A	12-07-2000	AT	249218 T	15-09-2003
		DE	69911159 D1	16-10-2003
		DE	69911159 T2	24-06-2004
		ES	2149750 T1	16-11-2000
		PT	1018340 T	31-12-2003

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/003348	31.03.2005	01.04.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K47/48 A61K31/515 A61P11/06 A61K31/198 A61K47/18

Applicant
F.HOFFMANN-LA ROCHE AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	see form PCT/ISA/210	Dullaart, A Telephone No. +31 70 340-3290